CALIFORNIA DEPARTMENT OF PESTICIDE REGISTRATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHYL PARATHION

SB 950-042, Tolerance #50468
Chemical Code 459

November 4, 1986
Updated 2/26/87, 6/05/90, 5/1/91 and 10/10/91

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effect
Chronic dog:	Data gap, inadequate studies, no adverse effect indicated
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, no adverse effect

Gene mutation:	No data gap, possible adverse effect indicated
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect [a]

Note, Toxicology one-liners are attached

In one-liner document and record number identifications below,
** indicates acceptable study
Bold face indicates possible adverse effect

Revision of 6/5/90 by Aldous and Gee, 5/1/91 and 10/10/91 by Gee
Filename: T911010

All relevant records on file as of 5/1/91 were considered for this Summary. These include record numbers through 096700 (Document 50468-063), Document -065 (record 089599) and one or more record numbers greater than 900000. C. Aldous, 6/5/90, Gee, 5/1/91 and 10/10/91.

[a] Although considered negative for delayed neuropathies in hens, there is evidence of neuromuscular effects in rodents.

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

COMBINED (CHRONIC/ONCOGENICITY)

RAT

** **50468-035 072066** Eiben, R., "Parathion study for chronic toxicity and cancerogenicity in Wistar rats (Administration in diet for twenty-six months)". Bayer AG, Toxicology Division, Wuppertal, final report completed Dec. 15, 1987 (sign-off by Director of the Institute für Toxikologie, Dr. E. Löser). Translation completed Jan. 7, 1988. Fifty rats/sex/treatment were placed on 2-year study: dosage groups of 0, 2, 8, and 32 ppm. There was no NOEL for cholinesterase (ChE) inhibition, since modest but statistically significant and dose-related plasma and RBC ChE inhibition was observed at the low dose of 2 ppm at some time periods. This dose could be considered a NOAEL for ChE inhibition, since substantial inhibition (i.e. > 20%) was limited to higher dosages, and since ChE-inhibition-related clinical signs were limited to 32 ppm females (particularly tremors). The NOEL for effects other than ChE inhibition was 8 ppm, based on reduced body weights in both sexes (ca. 20 g in females, 30 to 40 g in males); also on slightly increased mortality in 32 ppm females. In addition, there were two **possible adverse effects**: pancreatic exocrine tumors in males (with total incidence of 0, 0, 1, and 4 in controls through increasing dosage groups), and eye lesions (most definitively seen as increased degree of retinal atrophy in 32 ppm males and females). **Acceptable as a "combined" study**. Aldous, 5/24/90.

50468-051 085343 Eiben, R., "Historical incidence of tumors taken from studies with Wistar rats". (EPA MRID #40644704). March, 1986. This compilation is intended to supplement the 1986 Bayer rat parathion study, above. Data were presented on many tumor types. Data corresponding to the 22 studies on pancreatic tumors reported on p. 103 of the 1986 parathion rat study (Bayer AG) were presented in this report (identical numbers of affected rats were presented, with nearly always the same numbers of rats "at risk" as were provided in the parathion study. An explanatory letter (dated 5/18/90, located at the front of Document

50468-051) identifies all of these historical data to represent the timeframe 1980 to 1988. All were Bayer studies, all used the same source of animals as the parathion study (Winkelmann, Borchen), and all rats were Bor Wistar strain, as in the parathion study, above. Aldous, 5/23/90 (no CDFA worksheet).

50468-051 085344 Bombard, E. et al., "Spontaneous tumors of 2000 Wistar TNO/W.70 rats in two-year carcinogenicity studies". Published historical control data from JEPTO 7:35-52 (1986). All studies apparently were performed at Bayer AG, Institute of Toxicology, Wuppertal, F.R.G., or at nearby contract laboratories. All rats were bred at Winkelmann, Borchen (same source as 1986 Bayer AG Parathion study). All studies were started between 1973 and 1976. Six of the 11 studies were evaluated by the same pathologist. Variability was greater between studies evaluated by the same pathologist than between different pathologists. There were 9 islet cell tumors out of a total of 523 male rats examined (1.7%): none were found in females. One of these studies had incidence of 2/34 (6%), comparable to incidence in the cited Parathion study. Interestingly, no exocrine pancreatic tumors were noted in either sex in these 11 studies. Note that these data are of a somewhat earlier time period than the cited parathion study, and that these data are not part of the historical data submitted with the cited study. Aldous, 5/8/90.

50468-036 072061 Minor pagination corrections for 035:072066, above.

50468-028 050707 Preliminary report of study 035:072066, examined by C. Aldous, 2/26/87.

50468-004 011158 "Two Year Chronic Feeding Study of Ethyl Parathion in Rats." (Bio/dynamics, 1/23/84, Project No. BD-78-005, Ira W. Daley, Study Director). Incomplete version reviewed by J. Schreider, 3/12/85. Ethyl parathion (95.1%) fed in the diet to 60/sex/dose at 0, 0.5, 5.0 or 50 ppm with estimated intakes at 0, 0.02, 0.20 and 1.91 mg/Kg/day in males and 0, 0.03, 0.27 and 3.31 mg/Kg/day in females for 26-28 months; 60/sex/group; ChE NOEL= 0.5 ppm , other effects NOEL = 5 ppm (retinopathy at intermediate and

high doses; neuropathy at high dose only, thyroid adenomas in high dose males); **unacceptable** (early deaths in mid-dose males and high-dose females not explained; time-adjusted statistical analysis of pathology data is needed; more pathology narrative needed; discussion of hematology in high dose females needed; analytical methods for cholinesterase needed), possibly UPGRADEABLE with submission of the items requested by reviewer. J. Christopher, 10/16/85.

EPA ONE-LINER: oncogenicity follicular adenomas of thyroid 50 ppm, historical data required; tremors females 50 ppm, NOEL 5 ppm; abnormal gait females 50 ppm, NOEL 5 ppm; retinal degeneration females 50 ppm, NOEL, 5 ppm; depression all RBC values females 50 ppm, NOEL 5 ppm; depression plasma cholinesterase both sexes 5 ppm, NOEL 0.5 ppm; depression brain cholinesterase, both sexes, 50 ppm, NOEL 5 ppm; degeneration sciatic nerve 50 ppm, NOEL could not be determined. CORE GRADE: supplementary.

50468-008, 009, 010, 011, 012, 013, 014 34339, 34338, 34337, 34336, 34335, 34334 and 34333 Addenda to 11158.

50468-027 48663 Addendum to record #11158. Histopathology of peripheral nerve in middle and low-dose groups; data do not alter original one-liner or change the conclusions of that review (G. Patterson, 10/30/86).

50468-027 48664 Addendum to record #11158. These additional data on thyroid adenomas do not necessitate a revision in the one-liner or a change of the conclusions in the review (G. Patterson, 10/30/86).

CHRONIC

RAT

(See combined, rat, above)

DOG

50468-001, -065 014995, 089599 "Ethyl Parathion: One Year Feeding Study in the Dog." (F. E. Ahmed, Pharmacopathics Research Laboratories, 8/20/81). Ethyl parathion (lot AK 1103, 95.5%) fed in the diet at 0, 0.01, 0.03 or 0.1 mg/kg/day for one year; 8/sex/group; hematology, clinical chemistry and urinalysis prior to initiation and periodically until termination; no ophthalmology; no mortality; no adverse effects reported; there was a dose-related inhibition of cholinesterase activity, especially at 0.1 mg/kg with no clinical signs; initially reviewed as unacceptable (MTD not achieved, no justification of doses selected, tables of data cited in text were not included - last page was 145, Table #T-4.8.2 - incomplete report). Schreider, 3/12/85, updated 4/3/91, Gee. With the submission of the missing tables/appendices and the ophthalmology done in the 6-month study (see 096686), those defiencies are satisfied. What remains is the dose selection which is still considered a major deficiency. The study is **unacceptable and not upgradeable.** Gee, 10/8/91.
EPA ONE-LINER: ChE NOEL < 0.01 mg/kg (LDT) (RBC, plasma and brain ChE were inhibited); CORE GRADE: minimum.

Supplemental subchronic studies

001 016095 "Fourteen Day Feeding Study in the Dog." (Pharmacopathics Research Laboratories, 9/12/77) Ethyl parathion, 99.7%, was fed in the diet at 0 (diet), 1.5, 3.0 or 6.0 mg/kg/day to 2/sex/group, beagle dogs. Emesis was the major clinical sign reported in a dose-related incidence. All dogs survived. Gross necropsy only with no observations reported. **Supplemental** to 014995. No worksheet. Gee, 4/3/91.

001 016094 "Ethyl Parathion: Ninety Day Feeding Study in Dogs." (Pharmacopathics Research Laboratories, 3/6/78) Ethyl parathion, 99.4%, was fed in the diet for 90 days to beagle dogs, 4/sex/group, at 0 (diet), 0.3, 1.0 or 3.0 mg/kg b. wt. per day. No mortality. SGOT and SGPT were slightly elevated in the high dose males at 6 and 13 weeks but not in females. Plasma and RBC cholinesterase levels were decreased in a dose-related manner in males and

females with plasma showing a greater effect in both sexes. No inhibition of brain cholinesterase at 13 weeks. No compound-related necropsy or histological findings reported. ChE NOEL < 0.3 mg/kg b. wt./day. Systemic NOEL > 3.0 mg/kg/day. No diet analyses. **Supplemental** to 014995. No worksheet. Gee, 4/3/91.

063 096686 "A Six Month Oral Study of Ethyl Parathion in Dogs with Specific Emphasis on Ocular Effects." (J. E. Atkinson, Bio/dynamics, Inc., Project No. 89-3439, 3/21/91) Ethyl parathion, 98%, was given in gelatin capsules to 5 beagle dogs/sex/dose at 0 (corn oil), 0.0024, 0.0079 or 0.79 mg/kg/day for six months. Only gross lesions and the eyes were subjected to detailed examination. Cholinesterase activity was measured for plasma, RBC, pons and cerebellum of the brain, retina and ocular muscle. Electroretinograms were performed for functional impairment of the eye. No consistent findings other than cholinesterase inhibition at the high dose in both sexes were reported. The study is **supplemental** based on the design. Gee, 4/30/91.

ONCOGENICITY

RAT

(See also combined, rat, above)

50468-026 042902 (Gulf South Research, 1979, for NCI) Ethyl parathion, 99.5%, fed in the diet at 0, 32 or 63 ppm (TWA) to males and 0, 23 or 45 (TWA) to female Osborne-Mendel rats, 10/sex in concurrent controls and 50/sex/test group, for 80 weeks followed by 32-33 weeks of observation; onco NOEL < 32 ppm (TWA) in males and = 23 ppm (TWA) in females for increase in adrenal adenomas/carcinomas; **unacceptable** (no individual data, no periodic analysis of diet is presented, no hematology, clinical chemistry or urinalysis was performed, inadequate number of concurrent controls.) **Possible adverse effect:** Incidence of adrenal cortical adenomas/carcinomas in males was 0/9, 7/49 and 11/46 in control, low and high dose groups with 3/80 in pooled controls. In females, the incidence was 1/10, 6/47 and 13/42 with 4/78 in pooled controls. The incidence of pancreatic islet-cell carcinomas in males was 0/9,

1/49 and 3/46 with 0/79 in pooled controls. Body tremors in the second six months occurred in 25/50 of the high dose females. J. Gee, 11/3/86.

EPA 1-liner: No grade. Oncogenic NOEL = 32 ppm (male), 23 ppm (female) (increased adrenal cortical adenomas); systemic NOEL < 32 ppm (male), < 23 ppm (female) (decreased body weight, tremors, hyperexcitability).

ONCOGENICITY

MOUSE

50468-026 927590 (Gulf South Research, 1979, for NCI) Ethyl parathion, 99.5%, fed to B6C3F1 mice, 10/sex for concurrent control, 50/sex/treatment group, fed at 0, 80 or 160 ppm; males for 71 (low) or 62 (high) weeks, females for 80 weeks. No adverse chronic or oncogenic effects; some behavioral signs and decreased body weight gain in males (data in graph form only); onco NOEL $\geq$ 160 ppm, systemic NOEL cannot be determined from data as presented; **unacceptable** (no individual data, no hematology, clinical chemistry, urinalysis, no analysis of diet to verify doses, two doses only, inadequate number of concurrent controls, housing of animals from several studies in one room.) J. Gee, 11/3/86.

EPA 1-liner: No grade. Oncogenic NOEL > 160 ppm (HDT), systemic NOEL , 80 ppm (LDT) (depressed body weights, tremors, hyperactivity, and hyperexcitability.) NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/6/89) notes EPA classification as "Core Supplementary".

**** 060 (17 parts) 089300** "Carcinogenicity Study of Ethyl Parathion Administered by Dosed Feed to B6C3F1 Mice." (Page, J. G. and Heath, J. E., Southern Research Institute, Birmingham, Alabama, project A21-CRM-1, 2/21/91) Ethyl parathion, lot/batch #DK-7620/70818-01, 96.7%, was fed in the diet to B6C3F1 mice at 0, 60, 100 or 140 ppm for 18 months. There were 50/sex/group with satellite groups of 35/sex for control and 140 ppm doses. Due to technical error, 60 ppm groups received approximately 500 ppm days 300 to 307 of the study, resulting in a few deaths. Cholinesterase inhibition was measured at 10 days, 12 and 18

months in control and 140 ppm sentinel animals. Plasma, RBC and brain inhibition was significant at 140 ppm. Signs of cholinesterase inhibition (labored breathing, hypoactivity, tremors) were noted, especially early in the study. Body weights were lower at 100 and 140 ppm, with males more affected than females. A **possible adverse effect** is noted for systemic malignant lymphoma in males with incidences of 0/50, 0/50, 2/50 and 4/50 with increasing doses and a positive trend test of p = 0.008 - these incidences are within historical control values. The incidence of lung alveolar/bronchiolar adenomas in males is difficult to interpret because of the misdosing: 5/50, 13/50, 6/50 and 4/50 with increasing doses - no positive trend test. Study is **acceptable.** (Gee, 4/1/91)

REPRODUCTION

RAT

** 50468-006 011160 "A Two-generation Reproduction Study." (Biodynamics, Project 80-2457, 8/18/82). Ethyl parathion (95.1%) was fed in the diet at 0, 0.5, 5.0 and 25 ppm to CD rats for 14 weeks before mating the F0 parents and approximately for 18 weeks before mating the F1 parents; 2 generations; 15 males per group, 30 females per group; histopathology on 10/sex/group F1 adults and 5/sex/group F1 and F2 weanlings; gross postmortem exam for all F0 and F1 parents, all weanlings; diets analyzed for content and homogeneity; no adverse effects reported; parental NOEL = 5 ppm (decreased body weight gain, anogenital staining in 4/30 high dose females); **acceptable**. Schreider, 3/15/85, updated 4/3/91, Gee.
No EPA 1-liner.

TERATOGENICITY

RAT

** 50468/005 011161 "A Teratogenicity Study in Rats." (Biodynamics, project BD-82-081, 8/26/83). Ethyl parathion (95.1%, lot AK-1144) was tested at 0 (corn oil), 0.25, 1.0 and 1.5

mg/Kg/day by gavage on days 6-19 of gestation with 24 CD rats per group; doses were 85 - 106% of nominal; no adverse developmental effects reported; maternal NOEL = 1 mg/kg/day (decreased weight gain, mortality of 4/24 high dose dams - cause not stated); lacrimation - a cholinergic sign - was seen at increased incidence in all treatment groups at day 6 (2, 15, 14 and 17 for controls and increasing doses), at day 10 (6, 9, 16 and 18) and day 15 (3, 6, 20 and 14) - considered an acute reaction; developmental NOEL $\geq$ 1.5 mg/kg/day. **Acceptable**. Schreider, 3/14/85, updated by Gee, 4/3/91.

EPA ONE-LINER: Teratogenic NOEL >1.5 mg/kg (HDT); fetotoxic NOEL >1.5 mg/kg; maternal NOEL = 1 mg/kg (mortality, decreased weight gain, chromodacryorrhea); CORE GRADE: guideline.

50468-005 011162 Range finding study for 011161. Doses used were 0, 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg/day. Schreider, 3/13/85.

50468-016 036105 "Study for Embryotoxic Effects on Rats after Oral Administration." (Bayer, 9/4/84). Ethyl parathion (98.8%) tested at 0, 0.1, 0.3 and 1.0 mg/Kg/day by gavage on days 6-15 of gestation; NOEL: Maternal toxicity = 0.3 mg/Kg, fetotoxicity = 0.3 mg/Kg; **unacceptable** (no analysis of dosing solution, no presentation of test article assay, no individual necropsy data on dying animals, no individual clinical observations, insufficient explanation of the fetal examinations, insufficient explanation of experimental methods, no connection of malformations or skeletal variations with individual fetuses, no identification of dams with clinical observations), **upgradeable**. Schreider, 4/17/86.

RABBIT

** 50468-005 011163 "A Teratogenicity Study in Rabbits." (Biodynamics, Project BD-82-162, 11/4/83). Ethyl parathion (95.1%) was tested at 0 (corn oil), 1, 4, and 16 mg/Kg/day by gavage on days 7-19 of gestation, 18/group. No adverse effects were reported. Maternal NOEL = 1 mg/kg/day (weight loss and fur staining), developmental NOEL = 1 mg/kg/day (distended renal pelvis). **acceptable**. Schreider, 3/13/85.

EPA ONE-LINER: Teratogenic NOEL > 16 mg/kg (HDT); fetotoxic NOEL = 1 mg/kg (with mortality and renal pelvis distention reported at 4 and 16 mg/kg; maternal toxic NOEL = 1 mg/kg (decreased weight gain); CORE GRADE: guideline.

005 11164 Range finding study for 11163.

50468-016 036106 "Study of Embryotoxic Effects on Rabbits after Oral Administration." (Bayer, 2/15/85). Ethyl parathion (98.8%) was tested at 0 (0.5% Cremophor), 0.03, 0.1, and 0.3 mg/Kg/day by gavage on days 6-18 of gestation with 15/group. No adverse effects reported including no skeletal variations at any dose. **Unacceptable** (doses too low, no data on skeletal variations, no individual necropsy information, no individual fetal weights, no individual clinical observations). **Not upgradeable**. Schreider, 4/17/86.

MUTAGENICITY

GENE MUTATION

NOTE: From the limited data available in study 50468-036:072085, parathion is considered positive for gene mutation in mammalian cells, even though an acceptable microbial in vitro study was negative. There was a single trial with CHO/HGPRT in which there was a clear increase in mutation frequency at a low concentration. If a new study were to be conducted in the same cell system, using a similar concentration range and successfully overcoming miscibility problems, the replacement study would be cause for the mutagenicity data base to be re-evaluated. As of now, the data requirement is filled by Record #072060, with a possible adverse genotoxic effect in Record #072085. Gee, 6/5/90.

** 50468-036 072060 "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay." (Lawlor, T. E., Microbiological Associates, Rockville, MD; Study Number T5772.501014, 3/22/88) Ethyl parathion, technical grade, 97/98%, lot 70818-01, was tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and

TA100. Two trials with triplicate plates per concentration in each trial were run with and without activation with Aroclor 1254-induced male Sprague Dawley rat liver S9. Concentrations were 0 (DMSO), 667, 1000, 3333, 6667 or 10,000 µg/plate, nominal concentration. Slight to moderate precipitate was noted at 3333 µg/plate and higher. No evidence of an increase in reversion rates was reported. **No adverse effect. Acceptable.** Gee, 6/1/90.

50468-036 072085 "CHO/HGPRT Mutation Assay." (Yang, L. L., Microbiological Associates, Rockville, MD, Study Number T5772.332, 3/28/88) Ethyl parathion (97/98% technical) was tested for gene mutagenicity with Chinese hamster ovary cells in the presence and absence of activation with Aroclor 1254-induced male Fischer rat liver S9. Concentrations used were 0 (solvent and untreated), 0.03, 0.06, 0.1, 0.2 or 0.3 µl/ml of medium, duplicate cultures in a single trial. Cells were incubated with ethyl parathion for five hours followed by 7 - 9 days of expression time. They were then plated for selection of mutants with 6-thioguanine. Parathion was not fully miscible at 0.06 µl/ml and above. At 0.03 µl/ml, the mutation frequency (mutants/10^6 clonable cells) was increased significantly both with and without activation. **Possible adverse effect** of increase in mutation frequency. **Unacceptable, not upgradeable** (single trial). Gee, 6/1/90.

50468-016 036091 (Bayer, 6/25/80). Ethyl parathion (98.7-98.8%) tested at 0, 20, 100, 500, 2500, and 12,500 ug/plate +/- S9 on four strains of Salmonella - TA1535, TA1537, TA98 and TA100; 4 replicates; data suggest that there may be an effect but cannot evaluate; **unacceptable** (incomplete and mislabeled tables, mean values only, no repeat trial), **not upgradeable**. Gee, 4/21/86.

CHROMOSOMAL EFFECTS

** 50468-036 072087 "Micronucleus Cytogenetic Assay in Mice: Final Report." (Putman, D. L., Microbiological Associates, Bethesda, MD, Study No. T5772.122, 3/24/88) Ethyl parathion (97/98% technical), lot 70818-01, was given by intraperitoneal injection to male and female

CD-1 mice in a single dose. Doses were 0 (corn oil), 3, 13 or 26 mg/kg, 10 ml/kg. At 26 mg/kg, 31/40 were dead by 24 hours so the survivors were sacrificed for a 24-hour time-point. At the other doses, 5/sex were sacrificed at 24, 48 and 72 hours. One thousand polychromatic erythrocytes were scored per animal and the proportion of PCE's per total erythrocytes determined. It was necessary to run two attempts due to excess toxicity in the first trial (doses of 3, 17 or 34 mg/kg) and a problem with dosing solution preparation. **No adverse effect. Acceptable.** Gee, 6/4/90.

50468-036 072088 "Dominant Lethal Test on the Male mouse to Evaluate for Mutagenic Effect." (Herbold, B., Bayer AG, Institute of Toxicology, FRG, Report No. 14224, 1/15/86) Ethyl parathion (batch 230 300 004 - 008), 98.8%, was assayed for dominant lethal effects in male Bor: NMRI (SPF Han) mice. Fifty per group were given the vehicle (Lutrol) or 10 mg/kg ethyl parathion in a single oral dose. Males were mated 1:1 with untreated females, for 12 4-day mating periods. The dose selection was based on a preliminary test at 5, 10 or 20 mg/kg - all in the 20 mg/kg group died. Females were scored for corpora lutea, implantations, pre-implantation loss and living/dead implants. **No adverse effect reported. Unacceptable, possibly upgradeable** (no concurrent positive control group or acceptable substitute.) Gee, 6/4/90.

50468-016 036092 (Bayer, 3/29/82). Ethyl parathion (95.9%); 5/sex/group given 2 x 5, 2 x 10 or 2 x 20 mg/kg by oral gavage and sacrificed 6 hrs after second dosing; insufficient information to evaluate for possible effect; 3/10 deaths in mid dose and high dose was lost due to mortality; **unacceptable** (protocol does not conform to guidelines, problems with dose selection) **not upgradeable**. Gee, 4/21/86.

DNA DAMAGE/REPAIR

** 036 072086 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes." (Curren, R. D., Microbiological Associates, Rockville, MD, Study No. T5772.380, 3/28/88) Parathion (97/98%

technical), 95% purity, was tested with primary rat hepatocytes from a male Sprague-Dawley rat. Concentrations were selected from a preliminary trial measuring cytotoxicity by release of lactic acid dehydrogenase. Final concentrations used were 0 (DMSO and medium), 0.0001, 0.0003, 0.0006, 0.001, 0.003, 0.006, 0.01 and 0.03 µl/ml. The three highest concentrations were too toxic to score. Triplicate coverslips were exposed per concentration with 50 nuclei per coverslip scored by net nuclear grain counts from ^{3}H-thymidine incorporation. Dimethylbenz(a)anthracene was the positive control and induced significant unscheduled DNA synthesis. The was no evidence of UDS with parathion. **No adverse effect. Acceptable.** Gee, 6/4/90.

NEUROTOXICITY

No neurotoxicity study is required at this time. CDPR has reviewed the data on parathion effects on delayed peripheral neuropathies, (Oudiz, D. and Klein, A.K., "Evaluation of ethyl parathion as a toxic air contaminant", 1988, CDFA Report Number EH-88-5). These authors found that the potential of parathion to produce delayed peripheral neuropathies is very small. They cited hen studies involving single high doses or repeated moderate dosages, which did not lead to delayed peripheral neuropathies. They noted that one rat chronic study (Daley, I.W., 1984, Bio/dynamics Study No. 77-2055, CDPR Record 50468-004:011158) indicated some evidence of distal neuropathies at the high dose of 50 ppm. More recently, a rat chronic/oncogenicity study, which has been accepted by CDPR and EPA, was negative for neuropathies at the high dose of 32 ppm [see review of this study, (Eiben, R., "Parathion study for chronic toxicity and cancerogenicity in Wistar rats (Administration in diet for twenty-six months)", Bayer AG, Toxicology Division, Wuppertal, final report completed Dec. 15, 1987, CDPR record 50468-035:072066)]. The latter study found no indications of delayed neuropathies at the high dose of 32 ppm. Hens are considered better surrogates than rats to evaluate delayed peripheral neuropathies. Given the large body of negative data in hens, and recognizing the precautions which must be taken to prevent substantial parathion exposure because of its marked acute

toxicity, CDPR has no need of a hen neurotoxicity study to support SB-950 requirements at this time. Aldous, 5/25/90.

50468-036 072089 Neal, B., "Review of literature on the potential for delayed neurotoxicity associated with exposure to ethyl parathion". Author concludes that the vast majority of studies indicate that parathion is unlikely to elicit delayed distal neuropathy in humans. Many significant publications are reprinted in this record. It has been common practice to use ethyl parathion as a negative control for delayed distal neuropathy studies, since acutely toxic doses have repeatedly proved negative for delayed neuropathies in sensitive species. A single case report of a human exposure which was linked with paralysis of peroneus muscles has been noted for CDPR Hazard Assessment Group to consider (1950 article by von Petry, cited on p. 20 of 1976 NIOSH Criteria Document: Criteria for Occupational Exposure to Parathion). With the exception of that case report, and considering the substantial body of information on human exposure (which has occurred by accident or by experimental design), there is very little reason at this point to request further studies on possible delayed distal neuropathy potential in humans. Aldous, (no written CDPR review), 5/25/90.

MISCELLANEOUS

Risk assessment in Bioassay of Parathion for Possible Carcinogenicity by NCI.

SUPPLEMENTARY STUDY

062 096700 "A Three Month Oral Toxicity Study in Rats via the Diet with Ethyl Parathion to Investigate Ocular Effects and Cholinesterase Activity." (J. Atkinson, Bio/dynamics, Inc., Project No. 89-3469, 2/28/91) Ethyl parathion, technical, 98%, was fed in the diet for 3 months to female CD (Sprague-Dawley derived) rats at 0 (diet), 0.04, 0.4 or 4.0 mg/kg. The study was designed to determine the relationship between cholinesterase inhibition with dose and time and functional impairment of the eye as measured by electroretinography. There were

10 per group with pretest, 6 week and 3 month samplings and exams. Both light and electron microscopy were performed on the eyes. Although other tissues were saved, no histology was done. **Effect**; The results indicate that cholinesterase inhibition and functional impairment coincide and occur as low as 0.4 mg/kg. **Supplemental study**. Gee, 4/25/91.